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Shock volume: Patient-specific cumulative hypoperfusion predicts organ dysfunction in a prospective cohort of multiply injured patients

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Abstract

BACKGROUND: Multiply injured patients are at risk of developing hemorrhagic shock and organ dysfunction. We determined how cumulative hypoperfusion predicted organ dysfunction by integrating serial Shock Index measurements.

METHODS: In this study, we calculated shock volume (SHVL) which is a patient-specific index that quantifies cumulative hypoperfusion by integrating abnormally elevated Shock Index (heart rate/systolic blood pressure ≥ 0.9) values acutely after injury. Shock volume was calculated at three hours (3 hr), six hours (6 hr), and twenty-four hours (24 hr) after injury. Organ dysfunction was quantified using Marshall Organ Dysfunction Scores averaged from days 2 through 5 after injury (aMODS_{D2–D5}). Logistic regression was used to determine correspondence of 3hrSHVL, 6hrSHVL, and 24hrSHVL to organ dysfunction. We compared correspondence of SHVL to organ dysfunction with traditional indices of shock including the initial base deficit (BD) and the lowest pH measurement made in the first 24 hr after injury (minimum pH).

RESULTS: SHVL at all three time intervals demonstrated higher correspondence to organ dysfunction ($R^2 = 0.48$ to 0.52) compared to initial BD ($R^2 = 0.32$) and minimum pH ($R^2 = 0.32$). Additionally, we compared predictive capabilities of SHVL, initial BD and minimum pH to identify patients at risk of developing high-magnitude organ dysfunction by constructing receiver

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AUTHORSHIP

T.O.M. conceived the idea to calculate SHVL and designed the experiment. He was instrumental in all data collection and analysis and article preparation. T.M. conducted all SHVL calculations and aided in experimental design, data analysis and article preparation. C.M. conducted all organ dysfunction calculations and aided in experimental design, data analysis, and article preparation. B.L.Z. participated in experimental design, data analysis, and article preparation. In addition he facilitated patient enrollment. S.A.S. participated in experimental design, data analysis, and article preparation. In addition, she facilitated patient enrollment. T.M.B. designed and conducted the statistical plan. She aided in experimental design and helped write the article. G.E.G. designed the experiment, facilitated all data collection and analysis, and worked on article preparation.

DISCLOSURE

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operator characteristic curves. SHVL at six hours and 24 hours had higher area under the curve compared to initial BD and minimum pH.

CONCLUSION: SHVL is a non-invasive metric that can predict anticipated organ dysfunction and identify patients at risk for high-magnitude organ dysfunction after injury.

LEVEL OF EVIDENCE: Prognostic study, level III.

Keywords

Cumulative hypoperfusion; organ dysfunction; multiply injured patients; hemorrhagic shock

Organ dysfunction and adverse outcomes, such as nosocomial infection (NI), affect the clinical course of multiple injuries patients (MIPs).¹⁻⁴ Complications have a significant effect on both short-term and long-term outcomes.^{5,6} Early risk stratification of injury-related complications would offer treating physicians an expanded window to initiate interventional or supportive treatments to improve outcomes.^{7,8}

Hemorrhagic shock (HS) plays a foundational pathophysiologic role in organ dysfunction after injury.⁹⁻¹¹ Hemorrhagic shock causes immediate reductions in oxygen and nutrient delivery accompanied by reduction in waste removal from tissues.^{12,13} Prolonged HS eventually causes tissues to adapt anaerobic energy production which can lead to organ dysfunction. The physiologic consequences of HS are directly proportional to the magnitude and duration of hypoperfusion.^{12,13} Therefore, indices that account for both the magnitude and duration of HS have potential to stratify risks of complications in MIPs. Traditionally, researchers have quantified the magnitude of HS by measuring systemic markers that reflect the magnitude of anaerobic metabolism including pH and lactate and by calculating base deficit (BD). More recently, researchers have directly measured tissue-level oxygen saturation levels as a surrogate of shock.^{14,15} Collectively, the authors have shown that anaerobic metabolism and tissue-level oxygen saturation indices predict outcomes and organ dysfunction phenotypes.^{12,13,16-19} While serum levels of lactate are measured and BD is calculated at a single point in time, they reflect temporal accumulation of anaerobic metabolic products and accordingly provide insight on the duration and severity of HS. However, it is likely that values sampled at a single point in time do not fully account for the temporal component of HS and therefore, it remains unknown how well circulating concentrations of lactate, BD calculations, and systemic pH levels fully quantify cumulative hypoperfusion.

We recently introduced a metric that measures cumulative hypoperfusion, shock volume (SHVL).²⁰ Shock volume is calculated by integrating serial Shock Index (SI) (heart rate/systolic blood pressure) values during any prescribed acute injury/resuscitation time frame. Specifically, the duration and magnitude that SI values are above accepted thresholds of hypoperfusion (0.9) are integrated into an index that quantifies cumulative hypoperfusion.^{16,18,21,22} The goal of this study was to investigate the clinical utility of SHVL in predicting acute outcomes in a prospective cohort of MIPs. Our hypothesis was that SHVL would more closely correspond to the magnitude of organ dysfunction in MIPs compared with the traditional indices BD and pH. We do not routinely measure lactate at our institution, and

therefore lactate was not included in this study for comparison. To test our hypothesis, we calculated SHVL and measured BD and pH in a prospective cohort of MIPs and determined how these values corresponded to the magnitude of organ dysfunction and how well these values identified patients at risk of high-magnitude organ dysfunction.

PATIENTS AND METHODS

Patient Population

This study was approved by our institutional review board (IRB). We enrolled a consecutive prospective cohort of 100 blunt MIPs. Patients were aged 18 years to 55 years and met the following criteria: (1) presented as a full trauma activation defined by the general surgical trauma team with the attending surgeon present at the time of patient intake performing the initial resuscitation; (2) were admitted to surgical intensive care unit (ICU) from the emergency department or proceeded directly to surgery from the emergency department and were then admitted to surgical ICU. We excluded patients who died from traumatic brain injuries (TBI) within 48 hours or who had a Glasgow Coma Scale score of 7 or lower at presentation with no improvement after 48 hours. In addition, patients with preexisting hematologic or immunologic diseases were excluded. A consent waiver for 48 hours was allowed by our IRB to circumvent approaching critically injured patients or family members during the first 24 hours after injury. In the majority of cases, consent was obtained from a legal guardian between 24 hours and 48 hours after injury. If no consent was obtained by 48 hours after injury, all data were discarded. No patients who were originally enrolled into the study by guardian consent withdrew at later follow-up.

SHVL Calculations

Shock volume was calculated by integrating serial SI measurements into a value that accounts for both the duration and the magnitude of hypoperfusion during any prescribed period (Fig. 1). The SI values above 0.9 indicate hypoperfusion,^{16,18,21,22} and we chose this value as a hypoperfusion threshold for SHVL calculations. In our original work, we determined that SHVL calculated with a hypoperfusion threshold of 0.9 correlated more closely with organ dysfunction compared with using 1.2 or 1.5 as the threshold value.²⁰ Therefore, at any time point, the magnitude of hypoperfusion was determined by subtracting 0.9 from the SI values. For SI values that were less than 0.9, the SI value for SHVL calculations was set to zero.

Subsequently, incremental SI_i values were determined by averaging the corresponding adjacent SI values accounting for the 0.9 threshold. For example, in Figure 1 at time points c and d (within the dashed box), the SI values are 1.1 and 1.5, respectively. The incremental SI_i value for time interval between points c and d would equal: $[(1.1 - 0.9) + (1.5 - 0.9)]/2 = 0.4$.

Incremental SHVL_i values were calculated by multiplying the SI_i by the duration, in minutes, of the corresponding time interval. For example, in Figure 1, if $t(d) - t(c)$ was 15 minutes, the SHVL_i between time points c and d would equal $0.4 \times 15 = 6$ units of SHVL.

Finally, $SHVL_i$ values were integrated over an entire prescribed period T to yield a SHVL magnitude: $SHVL = \sum SHVL_i$ for $t = 0$ to T .

We calculated three distinct SHVL values during the initial 3 hr, 6 hr, and 24 hr periods (3 hr SHVL, 6 hr SHVL, and 24 hr SHVL). These three time points were chosen to quantify cumulative hypoperfusion during the initial resuscitation time frame and during the first injury day. We did not calculate SHVL values beyond 24 hr. The accuracy of SHVL measurements is affected by temporal sampling frequency of vital signs.²⁰ In the first 24 hr after injury, vital signs were typically recorded every 15 minutes during the first 8 hours to 12 hours, and rarely greater than a period of 60 minutes. During the second 24 hr after injury, vital sign sampling was notably less frequent and therefore we did not calculate SHVL beyond the first 24 hr after injury. *Organ Dysfunction:* The primary outcome was organ dysfunction quantified by the Marshall Multiple Organ Dysfunction Score (MODS).²³ The MODS integrates daily integer scores in six organ systems including pulmonary, cardiovascular, renal, hepatic, hematologic, and central nervous system. Day 1 (D1) MODS more closely reflected the injury magnitude compared with progression of organ dysfunction after injury and were not used in organ dysfunction calculations.^{1,24} We investigated daily MODS to develop an optimized index of organ dysfunction. We focused on MODS from D2 through D5 as this window corresponded to the temporal envelope in which patients either resolve injury or develop organ dysfunction.³ In addition, all resuscitative interventions and the majority surgical interventions occurred in this period. Individual daily MODS ($MODS_{D2}$; $MODS_{D3}$, $MODS_{D4}$, $MODS_{D5}$) and average MODS (aMODS) representing all possible means of combinations of sequential daily scores in D2 through D5 ($aMODS_{D2-D3}$; $aMODS_{D2-D4}$, $aMODS_{D2-D5}$; $aMODS_{D3-D4}$; $aMODS_{D3-D5}$; $aMODS_{D4-D5}$) were investigated for correspondence to clinical outcomes including duration of admission to surgical ICU (ICU_{Days}), duration of mechanical ventilation (MV_{Days}), and the presence of NIs.

Nosocomial infections were defined by CDC criteria.²⁵ Pneumonia was diagnosed by (1) the presence of a new or progressive radiographic infiltrate; (2) presence of at least two of three clinical features, fever ($>38^{\circ}C$), leukocytosis (>12 k) or leukopenia (<4 k) and purulent secretions; (3) confirmation by quantitative lower respiratory tract cultures via bronchoalveolar lavage. Bacteremia was defined by clinical symptoms of fever and increased cardiac index combined with white blood cell count greater than 12,000 or less than 4,000 and positive blood cultures. Urinary tract infection was defined by (1) at least one of the following signs or symptoms: fever higher than $38^{\circ}C$, suprapubic tenderness, costovertebral angle pain or tenderness, urgency, frequency, dysuria; (2) urine culture with no more than two species of organisms identified, at least one of which is a bacterium with 100,000 colony forming units or greater. Nosocomial infections were confirmed by the site principal investigator.

Combining MODS from D2 through D5 ($aMODS_{D2-D5}$) integrated the broadest set of information and demonstrated higher correspondence to ICU_{Days} , MV_{Days} , and NI compared with individual daily MODS or any other combinations of daily MODS. Therefore, $aMODS_{D2-D5}$ was chosen as our primary outcome for this study.

Data Analyses

To determine the clinical utility of aMODS_{D2-D5}, initially, we performed logistic regression of aMODS_{D2-D5} with ICU_{Days} and MV_{Days}. These analyses showed progressive increases in both ICU_{Days} and MV_{Days} in patients with aMODS_{D2-D5} of 4 or greater (Fig. 2). Accordingly, we defined high-magnitude organ dysfunction as an aMODS_{D2-D5} of 4 or greater and low-magnitude organ dysfunction as an aMODS_{D2-D5} less than 4. We compared differences in ICU_{Days}, MV_{Days}, and the incidence of NI in patients with an aMODS_{D2-D5} either less than 4 or 4 or greater using standard *t* tests. We further refined our analyses and compared differences in ICU_{Days}, MV_{Days} and NI in groups stratified by aMODS_{D2-D5} from 0 to less than 2, 2 or greater to less than 4, 4 or greater to less than 6, and 6 or greater with standard *t* tests.

Correspondence of 3 hr SHVL, 6 hr SHVL, and 24 hr SHVL with aMODS_{D2-D5} was determined by logistic regression. Logistic regression was also used to assess correspondence of initial BD (notation for BD will remain positive in this manuscript) and minimum pH with aMODS_{D2-D5}. Finally, we determined how changes in BD and pH that occurred during the initial 24 hours after injury corresponded to organ dysfunction. The maximum difference between lowest and highest pH and BD, the difference between the initial pH and BD and those obtained 6 hr after injury, and the difference between the initial pH and BD and those obtained 24 hr after injury were determined. These delta values (differences) were investigated for correspondence to aMODS_{D2-D5} by logistic regression.

Thresholds of 6 hr SHVL and 24 hr SHVL values identified on regression plots were used to construct receiver operator characteristic (ROC) curves to predict high-magnitude organ dysfunction. Likewise, ROC curves were also constructed to determine the utility of initial BD and minimum pH to predict high-magnitude organ dysfunction. Area under the curve (AUC), 95% confidence intervals, sensitivity, specificity, and odds ratios of each index threshold are reported for each predictive model.

RESULTS

Patient Population

We prospectively enrolled 100 consecutive MIPs from April of 2015 through September of 2016, capturing over 95% of eligible patients. The overall mortality for all 100 patients was 9%. Fifty-one of the 100 patients had TBI. Fifteen of 51 patients were subsequently excluded due to severe TBI. In addition, three patients who were initially enrolled were subsequently diagnosed with spinal cord injury and were excluded from analysis. One additional patient who sustained an iatrogenic air embolus resulting in cardiac arrest and death during a transthoracic endovascular aortic repair was removed from analysis. This yielded the final study cohort of 81 patients. Six of the nine deaths in the entire 100 patient cohort occurred in the 15 patients excluded for severe TBI. The other two deaths occurred in the remaining 81 patients for a mortality rate of 2.5% in the final study cohort. Demographics, traditional injury severity indices, resource utilization, and global outcomes for the final 81 patient cohort are shown in Table 1. In addition, six patients were on antihypertensive medications, three patients had diabetes mellitus (one type I and two type

II), and four patients had chronic obstructive pulmonary disease. No patients were on anticoagulation medicines, or had preexisting cardiac conditions including heart block, or had a cardiac pacemaker. All of these patients were included in the study.

Organ Dysfunction and Clinical Indices

There was a clear and abrupt increase in ICU_{Days} (Fig. 2A) and MV_{Days} (Fig. 2B) in patients with aMODS_{D2-D5} of 4. ICU_{Days} increased from 4.2 (standard deviation (s.d.) = 2.7) days in patients with aMODS_{D2-D5} less than 4 to 15.7 (s.d. = 7.4) days in patients with aMODS_{D2-D5} 4 ($p < 0.0001$) (Fig. 3A). Likewise, MV_{Days} increased from 2.2 (s.d. = 2.0) days to 11.9 (s.d. = 7.5) days in the same aMODS_{D2-D5} groups ($p < 0.0001$) (Fig. 3B). Finally, NI occurred in 18.8% of patients with aMODS_{D2-D5} less than 4 compared to 63.6% in patients with aMODS_{D2-D5} greater than 4 ($p < 0.0001$) (Fig. 3C). There were no differences in ICU_{Days}, MV_{Days}, or NI in patients with aMODS_{D2-D5} of 4 or greater to less than 6 compared with patients with aMODS_{D2-D5} of 6 or greater. These results demonstrated that aMODS_{D2-D5} was a clinically meaningful phenotype which effectively delineated low-magnitude organ dysfunction as aMODS_{D2-D5} less than 4 and high-magnitude organ dysfunction as aMODS_{D2-D5} of 4 or greater.

SHVL Versus Organ Dysfunction

Logistic regression of 3 hr SHVL ($R^2 = 0.48$; $p < 0.001$), 6 hr SHVL ($R^2 = 0.52$; $p < 0.001$) (Fig. 4A), and 24 hr SHVL ($R^2 = 0.49$; $p < 0.001$) (Fig. 4B) with aMODS_{D2-D5} demonstrated that SHVL values corresponded closely to the magnitude of organ dysfunction. Shock volume calculated at all three periods demonstrated higher correspondence to aMODS_{D2-D5} compared with initial BD ($R^2 = 0.32$) (Fig. 4C) and minimum pH ($R^2 = 0.32$) (Fig. 4D). In addition, SHVL at all time points demonstrated better correspondence with aMODS_{D2-D5} compared with the maximum delta values of BD ($R^2 = 0.2949$) and pH ($R^2 = 0.2633$), the 6 hr delta values of BD ($R^2 = 0.1499$) and pH ($R^2 = 0.0752$), and the 24 hr delta values of BD ($r^2 = 0.2897$) and pH ($R^2 = 0.2133$). Regression plots (Figs. 4A–B) identified thresholds of 6 hr SHVL of 40 and 24 hr SHVL of 70 where the incidence of high-magnitude organ dysfunction (aMODS_{D2-D5} 4) began to increase more rapidly. Similarly, we identified thresholds of initial BD 6 (Fig. 4C) and a minimum pH of 7.24 (Fig. 4D) as thresholds corresponding to increasing aMODS_{D2-D5} 4. Therefore, these thresholds were used to construct ROC curves and calculate odds ratios to predict patients who would develop high-magnitude organ dysfunction. The ROC curves for SHVL indices, initial BD and minimum pH and corresponding AUC, ORs, sensitivity and specificity to predict high-magnitude organ dysfunction are shown in Figure 5. Both 6 hr SHVL and 24 hr SHVL demonstrated higher AUCs compared with initial BD and minimum pH. In addition, 24 hr SHVL was more sensitive than any of the other indices for identifying patients at risk for aMODS_{D2-D5} 4. In summary, SHVL demonstrated greater correspondence with organ dysfunction compared to initial BD, minimum pH, and changes in BD and pH occurring during the initial 24 hr. In addition, SHVL more accurately identified patients at risk for high-magnitude organ dysfunction compared to initial BD and minimum pH.

SHVL Versus Infection Complications

Twenty-nine (35.8%) of 81 patients developed NI. Mean 3 hr SHVL in patients that developed NI was 36.2 (s.d. = 40.1) compared with 19.6 (s.d. = 28.0; $p = 0.054$) in patients who did not develop NI. Mean 6 hr SHVL in patients that developed NI was 59.6 (s.d. = 55.2) compared to 34.3 (s.d. = 41.1; $p = 0.036$) in patients who did not develop NI. Finally, mean 24 hr SHVL in patients that developed NI was 191.0 (s.d. = 199.9) compared to 107.1 (s.d. = 124.6; $p = 0.047$) in patients who did not develop NI. Seven patients developed nine surgical site wound infections which included two abdominal wound infections, one chest wound infection, and six extremity wound infections. The mean 3 hr SHVL, 6 hr SHVL, and 24 hr SHVL calculations in patients who developed surgical site wound infections were 58.9 (s.d. = 41.9), 100.6 (s.d. = 57.2), and 347.1 (s.d. = 251.9). These results demonstrate how high levels of cumulative hypoperfusion significantly extrapolate into risk of nosocomial and surgical site wound infections.

DISCUSSION

SHVL had increased correspondence with organ dysfunction compared to initial BD and minimum pH. In addition, SHVL had increased correspondence to organ dysfunction compared to changes in BD and pH that occurred in the first 6 hr to 24 hr after injury. SHVL measured at three distinct time intervals, and as early as three hours after injury, numerically accounted for nearly 50% of observed organ dysfunction ($R^2 = 0.48$ to 0.52 ; Figs. 4A–B). SHVL accounts for the entire time-magnitude hypoperfusion history specific to the individual patient within a prescribed period. For example, the 24 hr SHVL was informed by the entire SI data set in the initial 24 hr after injury and demonstrated the highest sensitivity and odds ratio of identifying patients at risk for high-magnitude ($\text{aMODS}_{\text{D2-D5}} \geq 4$) organ dysfunction. However, the 24 hr SHVL and 6 hr SHVL had effectively identical correspondence with the magnitude of organ dysfunction (Figs. 4A and B) and AUC indices for predicting patients who developed high-magnitude organ dysfunction. These observations likely reflect that the majority of patients in HS were successfully resuscitated within six hours after injury. The modest increases in sensitivity and odds ratio demonstrated by 24 hr SHVL for predicting high-magnitude organ dysfunction are consistent with clinical observations that patients who have occult hypoperfusion persisting 24 hr after injury are at risk for organ dysfunction, complications, and death.^{26–28} It is possible that the higher correspondence between SHVL and organ dysfunction compared with all of the measures of BD and pH reflects that SHVL is informed by a complete temporal set of data that accounts for the entire hypoperfusion history.

We did not compare SHVL with lactate only because we do not routinely measure lactate in our hospital. It is possible that lactate would have better correspondence to organ dysfunction, and lactate thresholds may have better predicted high-magnitude organ dysfunction compared with BD and pH measurements and any of the SHVL calculations. However, it is possible that circulating lactate serum values would parallel BD and pH measurements, and correspondence between lactate and organ dysfunction would be similar to correspondence of $\text{aMODS}_{\text{D2-D5}}$ with initial BD and minimum pH. Therefore, we cannot conclude that SHVL is a superior index to predict organ dysfunction compared with lactate.

Shock volume calculations would presumably be affected by preinjury demographics, hemorrhage severity, patient response to injury, and resuscitation interventions. During the study period, we used the same resuscitation strategy of two units of PRBCs: one unit of FFP for patients who received blood products. Our hospital has since evolved after the conclusion of this study to the 1:1:1 protocol of PRBCs: FFP: Platelets. Differences in response to resuscitation interventions would invariably be reflected in both the magnitude and rate of change of SHVL. However, we did not specifically account for changes in SHVL (or BD and pH) pertaining to individual resuscitation measures in this study. Therefore, it is not known if SHVL is an effective metric to judge resuscitation. In addition, our study population age bracket was purposely narrowed in an attempt to minimize confounding effects of preexisting medical comorbidities. Therefore, it is unknown how SHVL corresponds to organ dysfunction in patients older than 55 years or in patients with medical comorbidities particularly pertaining to cardiac disease. Finally, we studied trauma patients who were initially admitted to ICU, representing a bias toward more seriously injured patients. It remains unknown how SHVL risk-stratifies organ dysfunction in patients who were less injured and not initially admitted to a higher level of care.

The primary objective of this investigation was to determine if SHVL could accurately predict the magnitude of organ dysfunction. Therefore, it was important to quantify organ dysfunction using methods that were clinically relevant. Researchers have debated optimal organ dysfunction phenotypes for experiments similar to our study.^{1,4,5,10} There are multiple scoring systems that quantify organ dysfunction that are notably similar. Therefore, instead of comparing how SHVL, BD, and pH corresponded to organ dysfunction using different organ scoring systems, we adapted an alternative approach that integrated progression of daily MODS to investigate a temporally expanded signature of organ dysfunction. We chose to investigate MODS from D2 through D5 which is admittedly arbitrary, but this corresponded to the period in which resuscitation was completed and the majority of surgical interventions occurred. In addition, it corresponded to a timeframe in which nearly all patients either resolved their injuries or developed longer-term illness with prolonged admission to ICU, consistent with previous investigations.^{3,10,23,29} This approach identified a markedly stark cutoff value of $aMODS_{D2-D5}$ of 4 (Fig. 2) which delineated patients into groups of benign or complicated outcomes (Fig. 3). Patients who had an $aMODS_{D2-D5}$ of < 4 had little morbidity and resource utilization. In contrast, patients with an $aMODS_{D2-D5} \geq 4$ had significant increases in NI, ICU_{Days} and MV_{Days} . These data suggest that not only is $aMODS_{D2-D5}$ a meaningful phenotype of organ dysfunction, but this index could serve as a therapeutic endpoint to judge efficacy of resuscitative, surgical and supportive interventions in MIPs. Additionally, indices such as SHVL calculations that identify patients at risk of developing an $aMODS_{D2-D5} \geq 4$ could alert clinicians early in the injury course and expand treatment windows to optimize surgical and supportive interventions. Finally, SHVL can be calculated in real time without any invasive monitoring or laboratory facilities. It may be particularly applicable for austere conditions, such as forward echelons in military care (i.e., Role 2 facilities) to titrate evacuation decisions. Alternatively, software adaptations to standard vital sign monitoring can readily calculate and display changes in SHVL in real time on any standard ICU monitor. Ongoing changes in real-time SHVL measurements could be readily available to alert physicians and nursing personnel that patients are not

adequately resuscitated, or may be reverting back into HS after initial successful resuscitation. However, rigorous prospective investigation will be necessary to determine the clinical utility of SHVL.

Traditionally, multiple organ failure (MOF) using MODS has been defined as two consecutive days of a MODS greater than 5.³⁰ Therefore, MOF was present in 24 (29.6%) of 81 patients in this cohort. Twenty-three of 24 patients who were positive for MOF³⁰ in this series had high-magnitude organ dysfunction with an aMODS_{D2-D5} of 4 or greater. In contrast, there were 9 (15.8%) of 57 patients who did not meet criteria for MOF that had high-magnitude organ dysfunction with an aMODS_{D2-D5} of 4 or greater. In these nine patients, six (66.7%) developed NI, mean ICU_{Days} was 15.1 (7 to 31) days, and mean MV_{Days} was 13.2 (5 to 31) days. In this small sample of patients, this suggests that integrating organ dysfunction information over an expanded window better reflects clinical outcomes compared to the traditional definition of MOF by the Marshall Score criteria.

Shock volume accuracy is dependent on vital sign sampling frequency and accuracy of SI_i values. In patients with prolonged time between vital sign recordings, an aberrantly high or low SI value measured at the beginning or the end of the prolonged interval would be multiplied by a large time increment and inadvertently increase or decrease the SHVL_i calculation. In addition, inaccurate SI values would inadvertently affect the preceding and the subsequent SHVL_i calculations. For example, in a patient with a SBP of 100 and a prevailing HR of 80, the SI_i would be 0.8, and this measurement would minimize the two corresponding SHVL_i calculations. If the same patient's HR was transiently increased to 140 secondary to pain or an ICU-based intervention, the SI_i would increase to 1.4 and this would significantly increase both corresponding SHVL_i calculations. Finally, SHVL calculations assume that the SI threshold of 0.9 indicates hypoperfusion. Shock Index has been shown to predict mortality, transfusion requirements, and organ dysfunction, and has been shown to be equally as accurate as BD in predicting transfusion requirements.^{18,22} A recent review and meta-analysis have concluded that an SI of 0.9 was the best threshold for hypoperfusion.^{18,21,22}

In conclusion, SHVL is a measure of cumulative hypoperfusion generated from serial vital sign measurements. It is an effective tool that can predict the magnitude of anticipated organ dysfunction and stratify the risk of developing high-magnitude organ dysfunction in MIPs.

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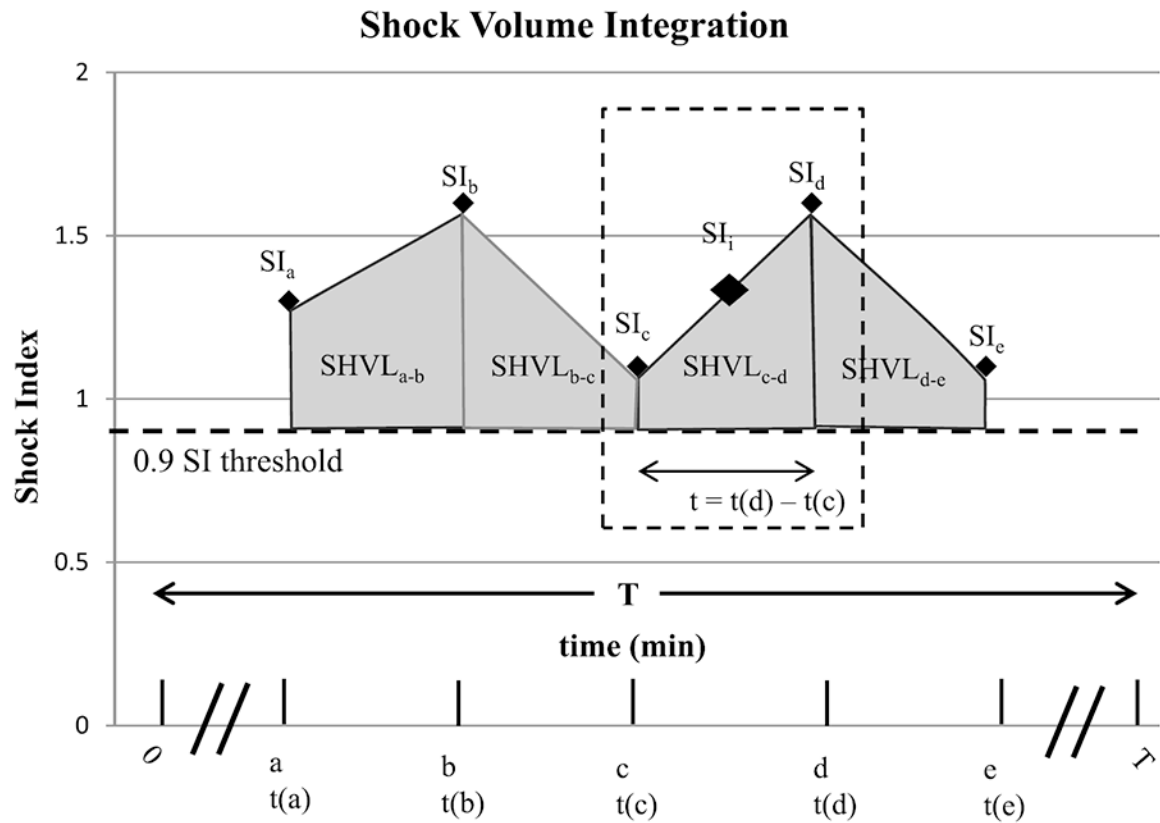


Figure 1.

Schematic depicting SHVL calculations. Five SI values (small black diamonds) are shown at five corresponding time points a through e (time points designated $t(a)$, $t(b)$, ...). Four distinct incremental $SHVL_i$ segments ($SHVL_{a-b}$, $SHVL_{b-c}$, $SHVL_{c-d}$, and $SHVL_{d-e}$) are depicted between time points a through e. The mean incremental SI_i value (above the 0.9 hypoperfusion threshold depicted by the dashed line) between time points c and d is illustrated by the large diamond within the dashed box. It is the average of the adjacent SI values, SI_c and SI_d . This SI_i value is multiplied by the time duration of the interval t ($t = t(d) - t(c)$ in minutes) to yield the incremental $SHVL_{c-d}$ value. For the prescribed time interval from 0 to T, all of the incremental $SHVL_i$ are summed to yield the SHVL. For example, for the 3 hr SHVL, all incremental $SHVL_i$ from admission until 3 hr after admission would be summed. In this figure, SHVL would include all $SHVL_i$ from 0 to T.

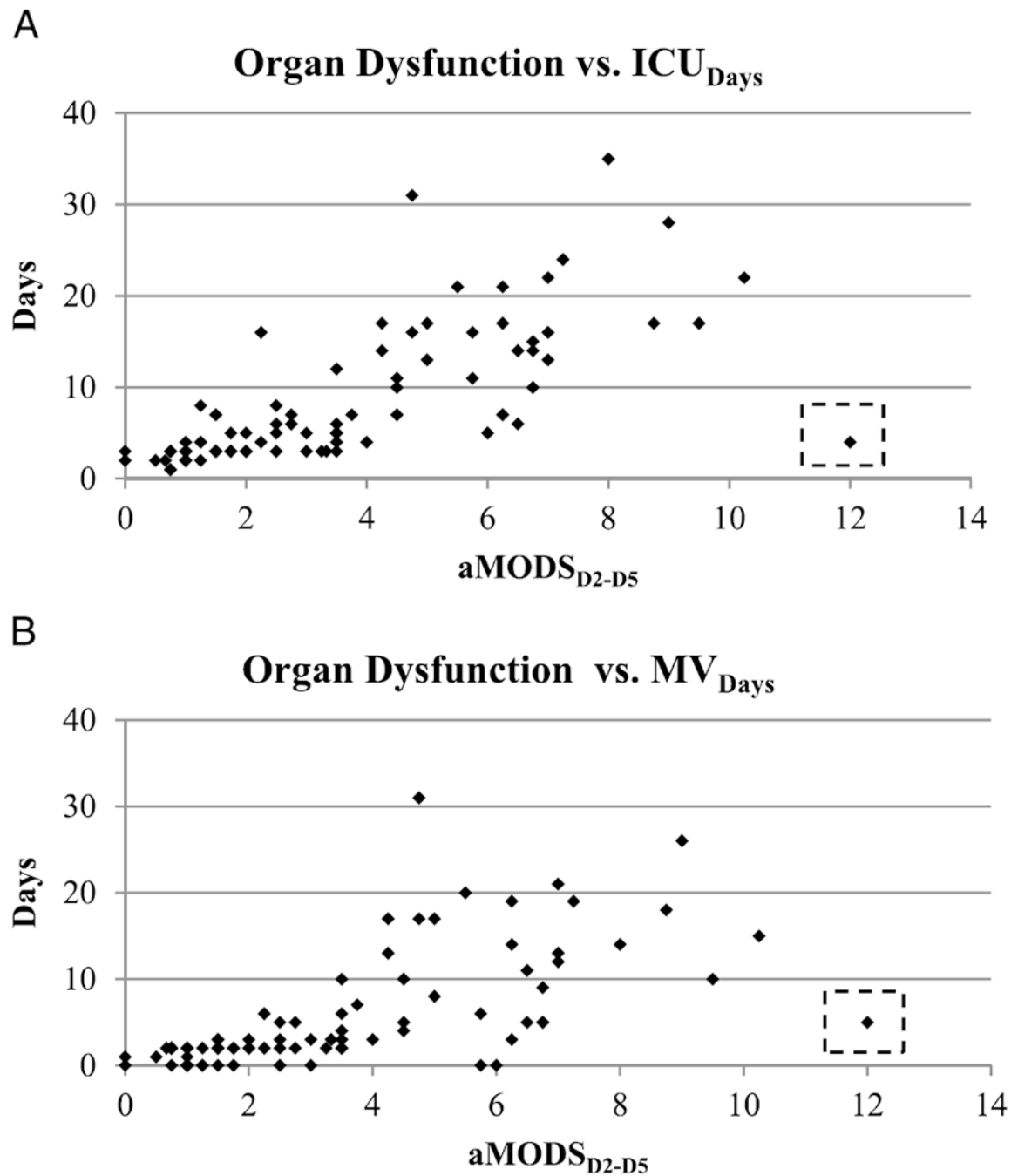
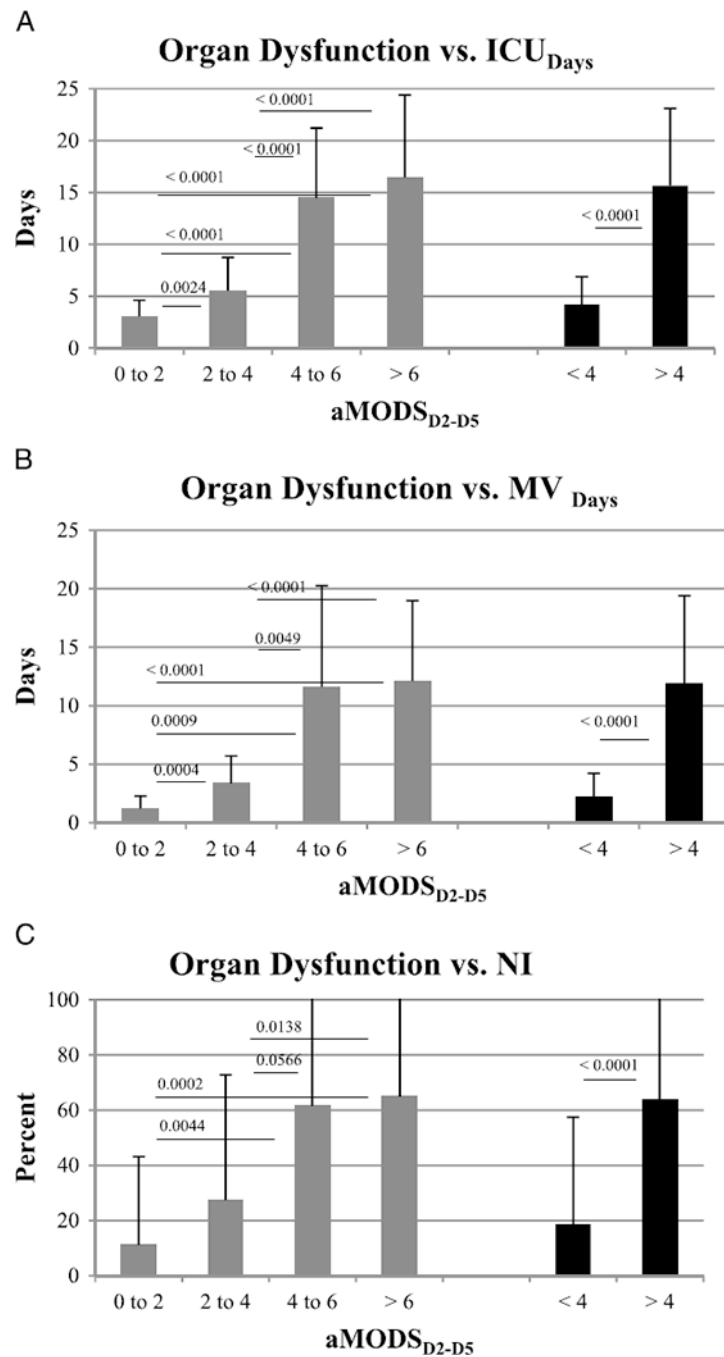


Figure 2.

Scatterplots demonstrate a marked increase in ICU_{Days} (*A*) and MV_{Days} (*B*) in patients who had an aMODS_{D2-D5} ≥ 4. Note the patient in the dashed box died on hospital day 5.

**Figure 3.**

Clinical indices demonstrated marked increases in duration of admission to intensive care (A), duration of mechanical ventilation (B), and the incidence of NIs (C) in patients with an aMODS_{D2-D5} ≥ 4 . Horizontal bars demonstrate differences considered statistically significant ($p < 0.05$) by t-testing.

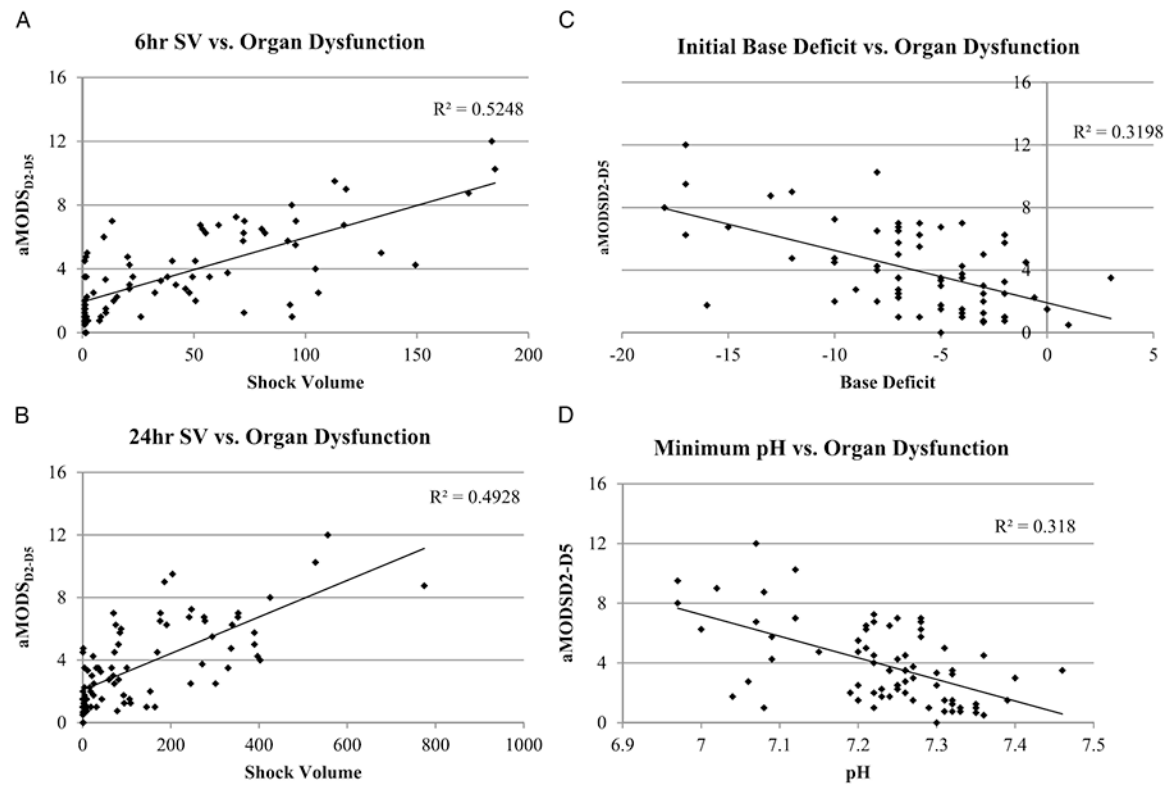
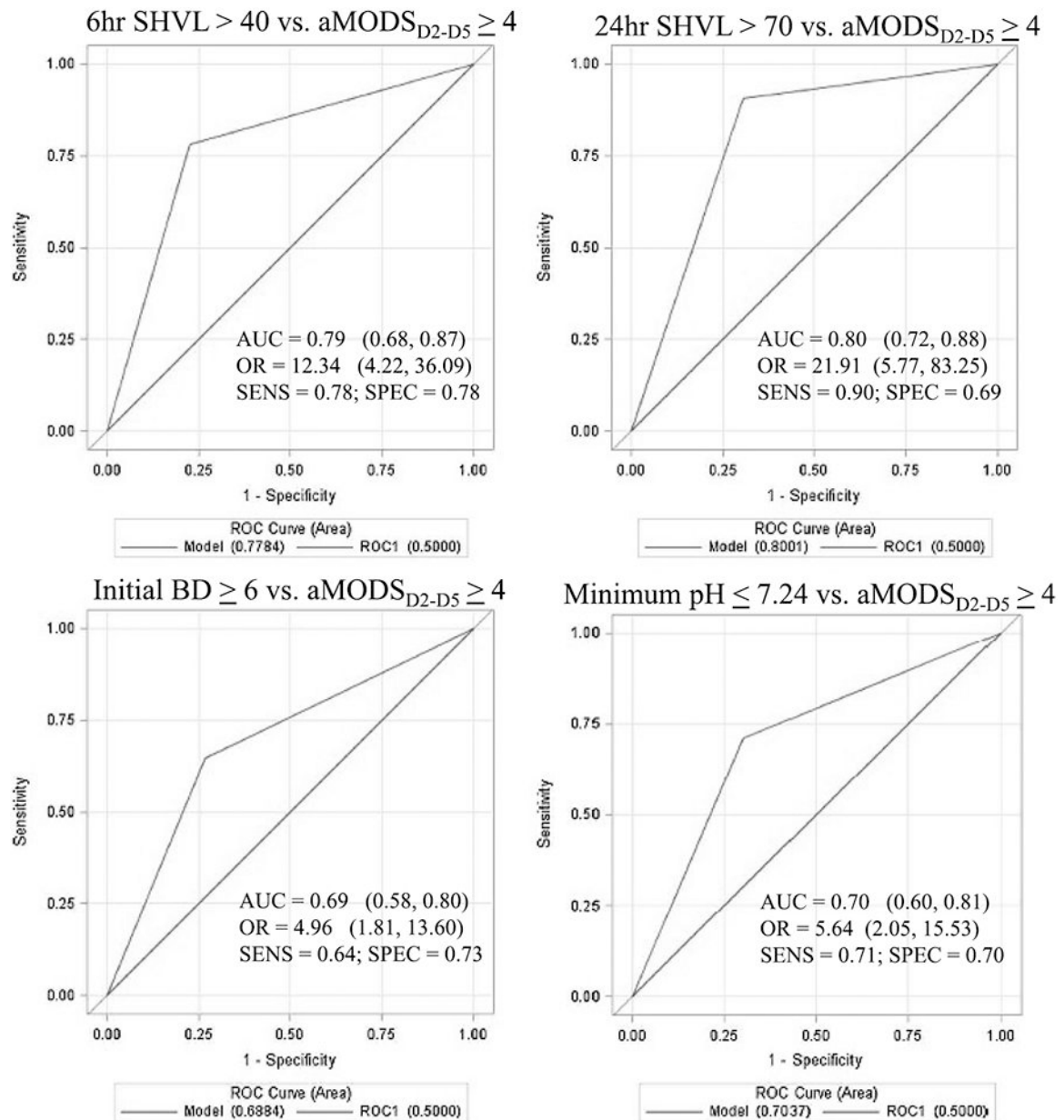


Figure 4.

Shock volume calculated at 6 hr (A) and 24 hr (B) demonstrated excellent correspondence to organ dysfunction (aMODSD_{2-D5}) with R^2 values from 0.49 to 0.52. Correspondence between SHVL and aMODSD_{2-D5} was greater than that seen with initial BD (C) and minimum pH (D). 3hrSHVL (data not shown) had similar correspondence with aMODSD_{2-D5} compared with 6hrSHVL and 24hrSHVL with an $R^2 = 0.48$.

**Figure 5.**

ROC curves comparing how 6hrSHVL and 24hrSHVL (top row) and initial BD and minimum pH (bottom row) predict patients who will develop high-magnitude organ dysfunction defined as aMODS_{D2-D5} ≥ 4. AUC (upper confidence limit, lower confidence limit), odds ratio (OR; upper confidence limit, lower confidence limit), and sensitivity/specificity are displayed. 24hrSHVL demonstrated the highest predictive power of high-magnitude organ dysfunction.

TABLE 1.

Cohort Demographics, Injury Severity and Resource Utilization

Age	36.5 (\pm 11.4) y
Sex	60 Male/21 Female
Injury Severity Score	31.3 (\pm 14.1)
Initial BD	6.1 (\pm 4.5)
Minimum pH	7.23 (\pm 0.10)
ICU _{Days}	8.8 (\pm 7.6) d
MV _{Days}	6.1 (\pm 6.9) d
Mortality	2/81 (2.5%)
MOF	24/81 (29.8%)